

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.



I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Label No. EL 951985842 US in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

On September 16, 2002

TOWNSEND and TOWNSEND and CREW LLP

By:

Dana Kane

PATENT
Attorney Docket No.: 02307E-088610
Client Ref. No. UC 98-306-2

RECEIVED

SEP 20 2002

TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Zuker *et al.*

Application No.: 09/361,652

Filed: July 27, 1999

For: NUCLEIC ACIDS ENCODING A
G-PROTEIN COUPLED RECEPTOR
INVOLVED IN SENSORY TRANSDUCTION

Examiner: Michael Brannock

Art Unit: 1646

DECLARATION UNDER 37 C.F.R.
§ 1.132 OF DR. CHARLES ZUKER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Charles Zuker, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

#24
JGJ
9/24/02

2. I received my Ph.D. from Massachusetts Institute of Technology. I am currently a Professor and Investigator, Howard Hughes Medical Institute, Departments of Biology and Neurosciences, School of Medicine, University of California at San Diego. I have been in this position since 1986. See resume, Exhibit A.

4. The above-referenced patent application claims isolated nucleic acids encoding GPCR-B3, also known as T1R1, a taste bud specific G protein coupled receptor involved in taste transduction.

5. I am an inventor of the above-referenced patent application. I have read and am familiar with the contents of the patent application. In addition, I have read the Office Action, mailed August 12, 2001, received in the present case. It is my understanding that the Examiner believes that this invention is supported by neither a specific, substantial, and credible asserted utility nor a well established utility as required by the United States Patent Laws.

6. This declaration is provided to demonstrate that, at the time the application was filed, one of skill in the art would recognize the utility of the present invention and would appreciate its real world context.

7. The present application discloses that the claimed nucleic acid, a full length cDNA, encodes a G protein coupled receptor ("GPCR") that is specifically expressed in taste buds of the tongue, and provides data demonstrating that the claimed protein is a functional G-protein coupled receptor. The present invention is therefore useful, e.g., for screening for taste modulators of a taste bud cell specific GPCR, for the identification of GPCR-B3 taste ligands, and as a specific marker for specialized taste bud cells of the tongue.

8. As described in the present specification, full length cDNAs that encode a taste cell-specific nucleic acids were cloned. Sequence analysis of the GPCR-B3 clone showed that it had the structure of a G-protein coupled receptor, with an extracellular domain, seven transmembrane domains, and a cytoplasmic domain (*see, e.g., Example I, page 56-57*). Subsequently, protein expression patterns were determined for GPCR-B3 using *in situ* analysis (*see, e.g., Example II, page 58, and Figure 3*). Figure 3 shows that the claimed nucleic acids express proteins that are specifically expressed in taste buds of the tongue.


9. Furthermore, the specification provides experimental data demonstrating that GPCR-B3 is a functional G-protein coupled receptor. Figure 4 shows the structure of a chimeric protein, comprising an extracellular domain of a murine MGluR1 receptor fused to the seven transmembrane domains and cytoplasmic domains of GPCR-B3. This chimeric GPCR construct was transfected into HEK cells, which were then stimulated with glutamate, the MGluR1 ligand. The HEK cells demonstrated an increase in intracellular calcium in response to the ligand, indicating that the chimeric GPCR couples to a promiscuous G protein and triggers calcium responses that are detectable using the indicator fura-2. The presently claimed GPCR-B3 nucleic acids therefore encode a G protein coupled receptor that is specifically expressed in fungiform and foliate cells of the tongue, which are taste bud cells, as described in the specification.

10. It would be apparent to anyone of skill in the art that GPCR-B3 is an excellent target for candidate compounds that modulate taste transduction. This use is not merely a "starting point for further research and investigation," but a direct assay for taste ligands and modulators of taste signal transduction. Furthermore, the claimed nucleic acids are specifically expressed in a unique subset of tongue cells, and the encoded proteins localize to the taste pore- the subcellular location for taste receptors. As such, they have specific and substantial utility as markers for specialized taste cells of the tongue. Such markers are useful for the generation of taste topographic maps the

elucidate the relationship between taste bud cells of the tongue and taste sensory neurons leading to taste centers in the brain. Applicants have therefore provided a nucleic acid that encodes a protein with known signaling activity and specific expression in a specialized sub-set of cells.

11. In view of the foregoing, it is my scientific opinion that one of skill in the art, at the time the application was filed, would immediately recognize the real world utility of the nucleic acids of this invention. Therefore, this invention is supported by a specific, substantial, and credible utility.

Date: 9/10/02

By: 

Charles Zuker, Ph.D.



CURRICULUM VITAE

NAME: CHARLES ZUKER

TITLE: Professor

DATE OF BIRTH: June 27, 1957; Arica, Chile

CITIZENSHIP: United States (May 3, 1996)

ADDRESS: Division of Biological Sciences and
Dept. of Neurosciences, The School of Medicine
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0649

TELEPHONE NUMBER: (619) 534-5528

FAX NUMBER: (619) 534-8510

INTERNET ADDRESS: czuker@ucsd.edu

RECEIVED
SEP 20 2002
TECH CENTER 1600/2900

EDUCATION

INSTITUTION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Universidad Catolica de Valparaiso; Chile	B.Sc., Honors	1977	Biology
Massachusetts Inst. of Technology; Boston	Ph.D.	1983	Biology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE

1993 - present Professor and Investigator; Howard Hughes Medical Institute
Departments of Biology and Neurosciences, School of Medicine
University of California, San Diego

1989 - 1992 Associate Professor and Associate Investigator
Howard Hughes Medical Institute, UCSD

1986 - 1989 Assistant Professor; Department of Biology, UCSD

1983 - 1986 Postdoctoral Fellow; Department of Biochemistry;
University of California, Berkeley

1977 - 1983 Graduate Student; Department of Biology; Massachusetts Institute
of Technology

Honors and Keynote Lectures (selected)

Whitaker Health Sciences Fund Fellow, Massachusetts Inst. of Technology, 1979-1980

Whitaker Health Sciences Fund Fellow, Massachusetts Inst. of Technology, 1981-1982

European Molecular Biology Organization Fellow, 1983

Jane Coffin Childs Memorial Fund for Medical Research Fellow, 1984-1986

McKnight Foundation Fund for Neuroscience Award, 1988-1991

Monsanto Speaker, St. Louis University, St Louis, MO, 1991

Broadhurst Foundation visiting lecturer, Cambridge, MA, 1991

Institute Speaker, Scripps Research Institute, La Jolla, CA, 1992

Keynote speaker, Stanford Neurosciences Program Retreat, Monterey, CA, 1992

Pew Scholars Award, 1988-1992

Alfred P. Sloan Award in Neurosciences, 1988-1990

March of Dimes Basil O'Connor Award, 1989-1991

Merck Lecturer, UC Berkeley 1992

Institute speaker, Roche Institute of Molecular Biology, Nutley, NJ, 1993

Keynote Speaker, Pharmacological Sciences Program, Vanderbilt University, Nashville, TN, 1994

Keynote Speaker, Stanford Medical Scientist Training Program, Stanford University CA, 1994

Lecturer in the Life Sciences, Northwestern University Medical School, Chicago, IL 1994

Howard Hughes Medical Institute, Lecture series to Institute employees, Howard Hughes Medical Institute, Chevy Chase, MD, 1996
Keynote Speaker, FASEB Summer Conference on "The Biology and Chemistry of Vision", Keystone, CO, 1997
Keynote Speaker, U. Penn Graduate programs in Biochemistry, Molecular Biology and Pharmacology. Philadelphia, 1998
Cogan Award, Association for Research in Vision and Ophthalmology, 1998
University Lecturer, UT Southwestern Medical School, 1999
Alcon Award for outstanding contributions to vision research, 1999
American Academy of Arts and Sciences, 2000

Study Sections and Advisory Boards (selected):

Member, Scientific Advisory Board, Pew Latin American Scholars Program, 1990 - present
Mechanisms of Development, 1991-present
Neuron, 1995-present
Member, American Cancer Society Postdoctoral Research Selection Committee, 1995-1999
Member, Scientific Advisory Board, Schepens Research Institute, Harvard University, Cambridge, MA, 1995 - present
Member, Review Panel, Howard Hughes Medical Institute International Grants Program, 1996
Member, National Research Council/ National Academy of Sciences advisory committee for the US and HHMI program in Latin America, 1997-
National Advisory Committee of The Pew Scholars Program in the Biomedical Sciences, 1997-
Member, NIH Visual Sciences C study section, Bethesda, MD, 1997-2000
Member, NIDCD Strategic Planning committee 1999-
Damon Runyon-Walter Winchell Cancer Fund Scientific Advisory Committee, 1999-
Current Biology, 2000-
Steering Committee, Alliance for Cellular Signaling, 2000-
Advisory board, Pew program in Science and Society, 2001-
Advisory board, NIH-wide initiative on mouse mutagenesis, 2001-

Publications (selected):

- Zuker, C., D. Misner, R. Hardy and G. Rubin (1988). Ectopic expression of a minor *Drosophila* opsin in the major photoreceptor cell class. *Cell* 55: 475-482.
- Feiler, R., W. Harris, K. Kirschfeld, C. Wehrhahn and C. Zuker (1988). Targeted misexpression of a *Drosophila* opsin gene leads to altered visual function. *Nature* 333: 737-741.
- Shieh, B.-H., M. A. Stamnes, S. Seavello, G. Harris and C. Zuker (1989). The *nina A* gene required for visual transduction in *Drosophila*, encodes a homologue of the cyclosporin A binding protein. *Nature* 338: 67-70.
- Schaeffer, E., D. Smith, G. Mardon, W. Quinn and C. Zuker (1989). Isolation and characterization of two new *Drosophila* protein kinase C genes, including one specifically expressed in photoreceptor cells. *Cell* 57: 403-412.
- Smith, D., B.-H. Shieh and C. Zuker. (1990). Isolation and structure of an arrestin gene from *Drosophila*. *Proc. Natl. Acad. Sci. (U.S.A.)* 87: 1003-1007.
- Huber, A., D. P. Smith, C. S. Zuker, and R. Paulsen (1990). Opsin of *Calliphora* peripheral photoreceptors R1-6: Homology with *Drosophila* Rh1 and posttranslational processing. *J. Biol. Chem.* 265: 17906-17910.
- Stamnes, M. A. and C. S. Zuker (1990). Peptidyl-prolyl *cis-trans* isomerases, Cyclophilin, FK506 binding protein, and *ninaA*: four of a kind. *Curr Opin Cell Biol* 2: 1104-1107.
- Stamnes, M.A., B.-H. Shieh, L. Chuman, G. L. Harris and C. S. Zuker (1991). The cyclophilin homolog *ninaA* is a tissue-specific integral membrane protein required for the proper synthesis of a subset of *Drosophila* rhodopsins. *Cell*. 65: 219-227.
- Smith, D. P., M. A. Stamnes and C. S. Zuker (1991). Signal transduction in the visual system of *Drosophila*. *Ann. Rev. Cell Biol.* 7: 161-190.
- Ranganathan, R., W. A. Harris and C. S. Zuker (1991). The genetics of phototransduction. *Trends in Neurosci.* 14: 486-493.
- Colley, N. J., E. K. Baker, M. A. Stamnes and C. S. Zuker (1991). The cyclophilin homolog *ninaA* is required in the secretory pathway. *Cell*. 67: 255-263.
- Ranganathan, R., G. L. Harris, C. F. Stevens, and C. S. Zuker. (1991). A *Drosophila* mutant defective in extracellular calcium-dependent photoreceptor deactivation and rapid desensitization. *Nature* 354: 230-232.
- Smith, D. P., R. Ranganathan, R. W. Hardy, J. Marx, T. Tsuchida, and C. S. Zuker (1991). Photoreceptor deactivation and retinal degeneration mediated by photoreceptor-specific protein kinase C. *Science* 254: 1478-1484.
- Cassill, J. A., M. Whitney, C. A. P. Joazeiro, A. Becker and C. S. Zuker (1991). Isolation of *Drosophila* genes encoding G protein-coupled receptor kinases. *P. N. A. S., USA* 88: 11067-11070.
- Ondek, B., R. W. Hardy, E. K. Baker, M. A. Stamnes, B. -H. Shieh and C. S. Zuker (1992). Genetic dissection of cyclophilin function: Saturation mutagenesis of the *Drosophila* cyclophilin homolog *ninaA*. *J. Biol. Chem.*, 267:16460-16466.

- Feiler, R., R. Bjornson, K. Kirschfeld, D. Mismar, G. M. Rubin, D. P. Smith, M. Socolich and C. S. Zuker (1992). Ectopic expression of ultraviolet-rhodopsins in the blue photoreceptor cells of *Drosophila*: Visual physiology and photochemistry of transgenic animals. *J. Neurosci.*, 12:3862-3868.
- Stamnes, M.A., S.L. Rutherford and C. S. Zuker (1992). Cyclophilins, a new family of proteins involved in intracellular folding. *Trends in Cell Biology*, 2:272-276.
- Zuker, C.S. (1992). Phototransduction in *Drosophila*: A paradigm for the genetic dissection of sensory transduction cascades. *Current Opinion in Neurobiology*, 2:622-627.
- Britt, S.G., Feiler, R., Kirschfeld, K. and Zuker, C.S. 1993. Spectral tuning of rhodopsin and metarhodopsin in vivo. *Neuron* 11:29-39.
- Dolph, P.J., R. Ranganathan, N.J. Colley, R.W. Hardy, M. Socolich, and C.S. Zuker (1993). Arrestin function in inactivation of G protein-coupled receptor rhodopsin in vivo. *Science*, 260:1910-1916.
- Dolph, P.J., H. Man-Son-Hing, S. Yarfitz, N.J. Colley, J. Running Deer, M. Spencer, J.B. Hurley, and C.S. Zuker (1994). An eye-specific Gb subunit essential for termination of the phototransduction cascade.; *Nature*; 370: 59-61.
- Kernan, M., D. Cowan and C. Zuker (1994). Genetic dissection of mechanosensory transduction: mechanoreception-defective mutations of drosophila. *Neuron*, 12: 1195-1206.
- Zuker, C.S. (1994). On the evolution of eyes: would you like it simple or compound?. *Science*; 265: 742-743.
- Baker, E.B., N.J. Colley, and C.S. Zuker (1994). The cyclophilin homolog ninaA functions as a chaperone forming a stable complex *in vivo*, with its protein target, rhodopsin. *EMBO*, 13: 101-110.
- Ranganathan, R., B. Bacsikai, R.Y. Tsien, and C.S. Zuker (1994). Cytosolic calcium transients: spatial localization and role in *Drosophila* photoreceptor cell function. *Neuron*; 13: 837-848.
- Rutherford, S. and C.S. Zuker (1994). Protein folding and the regulation of signaling pathways. *Cell*, 79:1129-1132.
- Plangger, A., D. Malicki, M. Whitney and R. Paulsen (1994). Mechanism of Arrestin-2 function in rhabdomeric photoreceptors. *J. Biol. Chem.*, 269:26969-26975.
- Shieh, B-H. and B. Niemeyer (1995). A novel protein encoded by the *inaD* gene regulates recovery of visual transduction in *Drosophila*. *Neuron*, 14:201-210.
- Wu, L., B. Niemeyer, N. Colley, M. Socolich and C.S. Zuker (1995). Regulation of PLC-mediated signalling *in vivo* by CDP-diacylglycerol synthase. *Nature*, 373:216-222.
- Colley, N.J., A. Cassill, E.K. Baker, and C.S. Zuker (1995). Defective intracellular transport is the molecular basis of rhodopsin-dependent dominant retinal degeneration. *PNAS*, 92:3070-3074.
- Ranganathan, R., D. Malicki and C.S. Zuker (1995). Signal transduction in *Drosophila* photoreceptors. *Ann. Rev. of Neurosci.*; 18:283-317.

- Ranganathan, R. and C.F. Stevens (1995). Arrestin binding determines the rate of inactivation of the g-protein-coupled receptor rhodopsin *in vivo*. *Cell*, 81:841-848.
- Zuker, C.S. (1995). Cell signalling - a taste of things to come. *Nature*, 376:22-23.
- Scott, K., A. Becker, Y. Sun, R. Hardy, and C. Zuker (1995). Gq protein function *in vivo*: genetic dissection of its role in photoreceptor cell physiology. *Neuron*, 15:919-927.
- Kernan, M. and C. Zuker (1995). Genetic approaches to mechanosensory transduction. *Current Opinion in Neurobiology*, 5:443-448.
- Zuker, C.S. (1996). The biology of vision in *Drosophila*. *PNAS*, 93: 571-575.
- Niemeyer, B.A., E. Suzuki, K. Scott, K. Jalink, and C.S. Zuker (1996). The *Drosophila* light-activated conductance is composed of the two channels TRP and TRPL. *Cell*, 85: 651-659.
- Corey, D.P. and C.S. Zuker (1996). Sensory systems, editorial overview. *Current Opinion in Neurobiology*, 6:437-439.
- Acharya, J.K., K. Jalink, R.W. Hardy, V. Hartenstein and C.S. Zuker (1997). InsP3 receptor is essential for growth and differentiation but not for vision in *Drosophila*. *Neuron*, 18: 881-887.
- Vinos, J., K. Jalink, R.W. Hardy, S.G. Britt and C.S. Zuker (1997). A G protein-coupled receptor phosphatase required for rhodopsin function. *Science*, 277:687-690.
- Tsunoda, S., J. Sierralta, Y. Sun, R. Bodner, E. Suzuki, A. Becker, M. Socolich and C.S. Zuker (1997). A multivalent PDZ domain protein assembles signaling complexes in a G protein-coupled signaling cascade. *Nature*, 388:243-251.
- Scott, K. and C. Zuker (1997). Lights out: Deactivation of the phototransduction cascade. *Trends in Biochemical Sciences*, 261:350-354.
- Scott, K., Y. Sun, K. Beckingham and C.S. Zuker (1997). Calmodulin regulation of *Drosophila* light-activated channels and receptor function mediates termination of the light response *in vivo*. *Cell*, 91:375-383.
- Scott, K. and C. Zuker (1998). TRP, TRPL and trouble in photoreceptor cells. *Current Opinion in Neurobiology*, 8(3):383-388.
- Acharya, J., P. Labarca, R. Delgado, K. Jalink and C.S. Zuker. (1998). Synaptic defects and compensatory regulation of inositol metabolism in inositol polyphosphate 1-phosphatase mutants. *Neuron*, 20(6):1219-1229.
- Tsunoda, S., J. Sierralta and C.S. Zuker (1998). Specificity in signaling pathways: assembly into multimolecular signaling complexes. *Curr. Opin. in Gen. and Dev.* 8: 419-422
- Scott, K., and C.S. Zuker (1998). Assembly of the *Drosophila* phototransduction machinery into a macromolecular complex shapes elementary responses. *Nature*, 395, 805-808
- Zuker, C and Ranganathan, R (1999). The Path to Specificity *Science* 283, 650-651
- Hoon MA, Adler E, Lindemeier J, Battey JF, Ryba NJ, Zuker CS (1999). Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity. *Cell* 96, 541-51

- Tsunoda, S., and C.S. Zuker (1999). The organization of INAD-signaling complexes by a multivalent PDZ domain protein in *Drosophila* photoreceptor cells ensures speed and specificity of signaling. *Cell Calcium*, 26/5:165-171.
- Walker, R.G., A.T. Willingham, C. Zuker (2000). A *Drosophila* mechanosensory transduction channel. *Science* .287:2229-2234
- Adler, E., M.A. Hoon, K.L. Mueller, J.Chandrashekar, N.J.P. Ryba and C.Zuker (2000). A novel family of mammalian taste receptors. *Cell* 100:693-702.
- Chandrashekar, J., K.L. Mueller, M.A. Hoon, E. Adler, L. Feng, W. Guo, C.S. Zuker and N.J.P. Ryba (2000). T2Rs function as bitter taste receptors. *Cell* 100:703-711.
- Kiselev, A., Socolich, M., Vinos, J., Hardy, R., Zuker, CS and Ranganathan, R.(2000). A Molecular Pathway for Light-Dependent Photoreceptor Apoptosis in *Drosophila*. *Neuron*, 28, 139–152.
- Sullivan KM, Scott K, Zuker CS, Rubin GM (2000) The ryanodine receptor is essential for larval development in *Drosophila melanogaster*.. *Proc Natl Acad Sci U S A*. 97, 5942-7.
- Tsunoda S, Sun Y, Suzuki E, Zuker C (2001) Independent anchoring and assembly mechanisms of INAD signaling complexes in *Drosophila* photoreceptors. *J Neurosci*. 2001, 21: 150-8.
- Scott, K, Brady, R, Cravchik, A, Morozov, P, Rzhetsky, A, Zuker, C and Axel, R. (2001) Chemosensory gene family encoding candidate gustatory and olfactory receptors in *Drosophila*. *Cell*, 104, 661-731:
- Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, and Zuker CS. (2001). Mammalian sweet taste receptors. *Cell*, 106, 381-390
- Nelson G, Chandrashekar J, Hoon MA, Feng, L., Zhao G, Ryba NJ, and Zuker CS. (2002). An Amino Acid Taste Receptor. *Nature* 416, 199-202